# A I D S TREATMENT N E W S

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## Contents

# AIDS Treatment News

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**Statement of Purpose:**
*AIDS Treatment News* reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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# Animal Retroviral Infections Suggest Third Kind of Potential Treatment: HIV Harm Reduction

Comment by John S. James

All the approved HIV treatments so far are antiretrovirals -- drugs that directly target some step in viral replication. In the future we may have another kind of treatment, immune-based therapy, which strengthen the immune system's ability to control HIV, instead of attacking the virus directly.

A third approach, less talked about so far, might be called HIV harm-reduction treatment -- preventing the virus from causing harm despite a continuing high viral load. This could work because HIV seems to cause most of its damage indirectly -- by the toxic tat protein, for example, or by dysregulation of immune responses leading them to kill normal cells -- rather than by killing infected cells, which the body could normally replace. If so, then ways to block the indirect damage might become a new kind of treatment. (We distinguish HIV harm reduction from immune-based therapies because the former would not

necessarily target the immune system at all -- and also because it would have to be tested differently, since it might not decrease viral load, which immune-base therapies might be expected to do.)

One observation supporting this way of thinking is described in an abstract at the recent conference of the Institute of Human Virology, September 9-13, 2002, in Baltimore.[1] Mark Feinberg of Emory University noted that in monkeys and other primates, all known retroviral infections in their natural hosts did not cause AIDS-like disease. But the same viruses, in primates that are not natural hosts, do cause persistent infection, loss of CD4+ T-cells, and susceptibility to opportunistic infections. And in these animals that do get sick, low viral loads and strong cellular immune responses predict slower disease progression -- as they do in humans with AIDS.

But at least some animals naturally infected with SIV (simian immunodeficiency virus) successfully control the infection in a very different way. In the sooty mangabey monkey, for example, the immune system does not suppress viral load, which stays high, yet the animal does not become ill. From the abstract:

"... Surprisingly we have found that SIV-infected sooty mangabey monkeys do not develop AIDS despite high level virus replication, short longevity of infected cells and limited anti-SIV specific cellular immune responses.... Interestingly, an attenuated host immune response to the infection is manifest from early times during primary infection, suggesting that sooty mangabey evolution has selected for a limited, rather than an aggressive, host response. In all, these data suggest that the direct consequences of high level virus replication alone cannot account for the progressive CD4+ T cell depletion leading to AIDS, and that active antiviral cellular immune responses may not always be beneficial. Indeed, SIV-infected sooty mangabeys may be spared, by their failure to mount significant antiviral immune responses, much of the indirect bystander damage seen in pathogenic primate lentivirus infections that both contributes to accelerated CD4 depletion and compromises host immune regenerative capacity. In contrast, following zoonotic transmission of SIV to non-natural hosts, the generation of active but incompletely effective immune responses may indirectly both increase the magnitude of overall T cell destruction and reduce the host immune regenerative capacity, thereby leading to the development of progressive immune deficiency as T cells lost to cumulative direct and indirect consequences of virus infection are not replaced."[1]

## How to Proceed

A treatment that prevents AIDS by reducing damage from HIV might be hard to recognize. It might not decrease viral load at all, or even increase it. The ultimate proof would be that people would not get sick over a long period of time. But it would probably be impossible to conduct clinical trials in the straightforward way -- randomly assigning patients to antiretrovirals with or without the new treatment -- because the effectiveness of antiretrovirals has made it almost impossible to run clinical-endpoint trials. Instead, new drugs today are approved by their effect on viral load, an endpoint that would not work in this case. (In fact, if an existing drug for some other medical purpose happened to work this way and prevent the development of AIDS without lowering viral load, we would probably not know it, even if many patients with HIV had used the drug coincidentally.)

How then might it be possible to get a handle on the development of this kind of drug? Here are some possible approaches:

* Many patients have "discordant" viral load and CD4 counts. Instead of fitting the usual pattern of having higher CD4 counts if they have low viral load or vice versa, they either have a high CD4 count despite a high viral load, or a low CD4 count even though their viral load is low.

These two kinds of discordant patients could be compared to each other, to look for differences in how they respond to HIV infection. What could be learned from patients who can tolerate a high viral load and still maintain a high CD4 count -- especially those who remained healthy despite having the high viral load for a long time? If the mechanisms could be identified, perhaps some kind of pharmaceutical intervention could help other patients do likewise.

If there are some patients who, like the sooty mangabeys, are long-term non-progressors despite having a high viral load, we probably would not have recognized them. Instead we would have treated their viral load, and attributed non-progression to the treatment. But these patients might be identified by careful examination of their medical records.

* Basic research could look for the mechanisms involved, either in sooty mangabeys, other animals, or in any humans known to tolerate a high HIV viral loads and remain healthy.

Of course differences in the virus as well as the host could be responsible for reduced disease progression despite high viral load. But still the host somehow avoids disease even though the virus reproduces well and does cause disease in non-native hosts.

* For many years some physicians and researchers were interested in immune suppressive drugs to treat HIV. Their experience should be reviewed -- especially since sooty mangabeys seem to have evolved an effective defense against AIDS that includes a notably unaggressive immune response. Existing drugs may be too non-selective or have too many side effects for widespread use. More selective immune-suppressive drugs could be developed.

* Once a candidate harm-reduction drug is identified, it could be tested to see if it improves the health of patients who cannot control the virus with any existing treatment. Since their viral load cannot be controlled in any case, an experimental treatment to reduce viral damage could ethically be tested while the viral load stays high (necessary to see if the new treatment worked). A placebo control would be used since there is no approved HIV harm-reduction treatment. The volunteers could either take antiretrovirals or not as they chose. The study could look for T-cell count increases, reduction of symptoms believed to be caused by the high viral load, and/or other evidence of clinical improvement. Such endpoints could show significant change quickly in a small number of patients (unlike the "clinical endpoint" of disease progression, which requires hundreds if not thousands of volunteers because it counts low-probability, all-or-nothing events instead of measuring continuous data on everybody).

A treatment that prevented viral damage without reducing viral load would not have the public-health advantage of antiretroviral treatment in making patients less likely to transmit the virus to others. But in practice, this kind of treatment would probably be combined with antiretrovirals for maximum benefit, so the risk of transmission would still be reduced.

A possible advantage of HIV harm

reduction is that HIV develops resistance to all known antiretrovirals -- and to the body's immune responses as well. But a harm-reduction treatment would create different evolutionary incentives, as HIV variants would not need to evade either the therapy or the body's defenses in order to survive. They could do best by not provoking the immune system. And in the sooty mangabey example the viral load does not increase without limit until it kills the animal; there is still a setpoint, still a limit, and the animal remains healthy. So a harm-reduction treatment may also allow relatively harmless viruses (which would have an advantage here) to help crowd out more dangerous ones.

Perhaps such reasons explain why animals apparently evolved a strategy of maintaining health by preventing harm, even from continuous high levels of viruses still able to cause disease in other species. Human long-term non-progressors (at least those who have been identified) use a different strategy, of aggressive immune defense that keeps viral replication low enough to greatly delay escape from immune control. It seems likely that the former approach is the better one for controlling a virus that can mutate so rapidly. Possibly some patients are already benefiting from it, but under current medical and research practices we do not see them. For where viral load testing is available, treatment is available too, and almost no one gets viral load tests repeatedly unless they plan to treat a high viral load. Usually antiretroviral treatment would reduce the viral load and be credited for non-progression. And experimental HIV therapies that fail to lower viral load are not studied today.

As a result, a new kind of potential treatment for AIDS may have been overlooked.

### References

1. Feinberg M. Ignorance is bliss: how the natural hosts for SIV infection remain healthy despite long-term, high-level virus replication. *Journal of Human Virology.* 2002; volume 5, number 1, abstract #8.

## T-20 (FUZEON) Gets Priority Review

On October 11 Roche and Trimeris, Inc. announced that the FDA had granted priority review to FUZEON (TM) (generic name enfuvirtide, formerly known as T-20). This means that the FDA plans to review the application for approval in six months, and announce the results by March 16, 2003 (six months after the application for approval was submitted).

Enfuvirtide works differently from any currently approved HIV drugs: it blocks a step in the process by which HIV fuses with a cell membrane and enters the cell. Since it has an entirely different mechanism of action, virus that has become resistant to approved drugs will not automatically be resistant to this one. However, resistance to enfuvirtide does develop, as with other antiretrovirals. This drug also must only be used in combination treatments, never alone.

Enfuvirtide must be injected twice a day, can be difficult to use, and is

difficult to manufacture so it will probably be expensive. For these reasons it will likely be used mainly by patients who do not have other good options.

## ICAAC Clinical Trials Review Available

ICAAC, the Inter-Science Conference on Antimicrobial Agents and Chemotherapy, was held this year in San Diego, September 27 - 30. This annual conference focuses mainly on the development of new antibiotics and antivirals. On October 11 HIVandHepatitis.com published a review of the HIV clinical trial presentations at ICAAC, by Charles Hicks, M.D.; it is available at:
http://www.hivandhepatitis.com/2002conf/iccac2002/pages/35.html

Some of the topics:

* Atazanavir, an experimental protease inhibitor being developed by Bristol-Myers Squibb, was compared in a large international trial with efavirenz (brand name Sustiva -- or Stocrin in some countries);

* 3TC (Epivir) was successfully dosed for once-daily use;

* Coviracil, an experimental nucleoside reverse-transcriptase inhibitor, was compared with d4T; and

* For certain advanced patients, a combination of amprenavir (Agenerase) and lopinavir plus ritonavir (Kaletra), with some extra ritonavir (Norvir) added to overcome an interaction that would reduce the levels the other two drugs, appeared to work well.

All of these trials showed promising results that may improve HIV treatment in the future.

## Hepatitis C: FDA Public Meeting on Peginterferon Plus Ribavirin, Nov. 14

On November 14 the Antiviral Drugs Advisory Committee will review the application by Hoffmann-La Roche for approval of peginterferon alfa-2a combined with ribavirin. The meeting will include time for public comment, and comments can also be submitted in writing. If you want to address the committee you need to notify the staff before November 6 and submit a brief written statement about your presentation. Written statements to the Committee should be submitted by November 6.

The meeting will be held November 14, 2002, from 8:30 a.m. to 4 p.m. at the Holiday Inn, Versailles Ballroom, 8120 Wisconsin Avenue, Bethesda, MD. This location is near Washington D.C. and easily reachable by the Red Line subway.

More information is available from the FDA Advisory Committee Information Line, 1-800-741-8138 or 301-443-0572. You will be asked to enter a code; the code for the Antiviral Advisory Committee is 12531.

### Comment

We have heard that peginterferon will be approved as a single drug soon, maybe this week. The Advisory Committee will consider the combination with ribavirin. Our understanding is that Roche plans to sell its peginterferon alone as well.

FDA advisory committee meetings are often the best place to learn in-depth information about a new drug before it is approved. They are not called for every new drug application, only for those that present new, difficult, or particularly important issues. Usually a transcript and a summary appear later on the FDA

Web site.

The FDA is not required to follow the recommendations of its advisory committees, but it almost always does.

# Anti-HIV Factor Discovered

by John S. James

On September 26 scientists at the Aaron Diamond AIDS Research Center (ADARC) announced that they had identified a significant contributor to a long-sought antiviral factor, secreted by certain CD8 T-cells, that inhibits HIV replication.[1] This work does not change treatment now, but could lead to the development of a new class of HIV drugs. It was widely reported in the press.

The research team at ADARC, headed by Linqi Zhang, believes that this factor includes three previously known chemicals called alpha defensins. Through various tests, they found that these chemicals were produced by stimulated CD8 cells of three of the long-term non-progressors they are studying (they picked their three best non-progressors among their patients, in order to have the best chance of identifying how their cells are able to keep HIV in check). After the chemicals were identified -- with the help of a protein-chip technology that allows rapid, sensitive testing -- it was found in laboratory tests that antibodies to those chemicals could largely eliminate the anti-HIV activity of those cells -- helping to confirm that an anti-HIV factor is really these three defensins.

Only one to two percent of HIV patients are long-term non-progressors. Since 1986 it has been known that their cells can produce some substance or substances that inhibit HIV.[2] In 1995 it was shown that some of the activity was due to three other chemicals called beta chemokines. But the beta chemokines only block some HIV viruses, those that use the CCR5 receptor on the CD4 cell to enter the cell -- not viruses that use the CXCR4 receptor, which often evolve later in HIV infection.

The defensins are believed to block all HIV, and to act through a completely different mechanism -- possible involving viral transcription, instead of viral entry into the cell. These chemicals have been found not only in long-term non-progressors but in at least some healthy uninfected persons as well, and in several primate species. However they are seldom found in HIV patients who are not non-progressors.

The defensins would be very difficult to use as drugs, if they could be used at all. But when their action is better understood, it may be possible to devise other treatments that have the same effect. Another approach would be to maintain and enhance the body's ability to produce defensins. Either kind of treatment might convert patients into long-term non-progressors who would not become ill despite HIV infection.

## References

(1) Zhang L, Yu W, He T and others. Contribution of human alpha-defensin-1, -2, and -3 to the anti-HIV activity of CD8 antiviral factor. *Science Express*. September 26, 2002.

(2) Walker CM, Moody DJ, Stites DP, and Levy JA. CD8+ lymphocytes can control HIV infection in vitro by suppressing virus replication. *Science.* December 19, 1986; volume 234, number 4783, pages 1563-1566.

# Retroviruses

# Scholarship, Community Press, Other Deadlines Soon

by John S. James

The annual Retroviruses conference, one of the world's most important scientific meetings on HIV, will not take place until February 2003, but scholarship and other deadlines are approaching. For community members without an accepted scientific abstract, the scholarship or community press applications are the only way to get into this meeting. Therefore some will need to apply for the scholarship whether or not they need the money.

This year the 10th Conference on Retroviruses and Opportunistic Infections will be held in Boston for the first time, at the Hynes Convention Center, February 10-14, 2003.

## Deadlines by Date

* For scientists, abstracts are due October 23 at 5:30 Eastern time (except late breakers).

* Also for scientists, the Fellow Travel Grant applications are due October 23.

* For international scholarships, the application deadline is November 1.

* For U.S. community scholarships, the deadline is November 8.

* For community press, the deadline is also November 8.

* Preferred registration and housing for invited speakers and authors of accepted abstracts (two per abstract) is open November 18 - 29.

* Registration for other researchers and clinicians (without an accepted abstract) is open December 2 - January 10. *Caution* -- sometimes this conference fills almost immediately; in case that happens these applications must be sent as soon as this period begins. This year the conference will accept 3,800 registrations.

* The late breaker abstract deadline is January 6 at 5:30 Eastern time.

Be sure to check the conference Web site, http://www.retroconference.org, to confirm these dates and to get the forms and other information needed to apply.

# Treat-Your-Workers.org; International Coca-Cola Protest October 17

by John S. James

"AIDS is the crisis of our generation, and we will be defined by our response to it. Years from now, we will have to answer to our own children: did we stand by as millions died, or did we take action? We have a chance to make a real difference in shaping the outcome of this pandemic. We hope you will join us in this endeavor." From Student Global AIDS Campaign, cover letter transmitting *The Coca-Cola Campaign: A Manual for Student Organizers*.

Since a July 2002 announcement in Barcelona during the international AIDS conference there, activists in Africa, the U.S., and Europe have called for a global day of protest against Coca-Cola on October 17, asking for better health coverage for African workers and their families. Behind this protest are several developments.

Coca-Cola already provided health coverage including antiretrovirals to its